C. F. FLUHMANN, M. D. (Stanford University Hospital, San Francisco).—The infections of the cervix uteri, as Doctor Bath has pointed out in his article, are a very important clinical manifestation of pelvic inflammatory disease. Although I question very much whether the actual pathologic process in the cervix itself can lead to many changes in the body of the uterus, there is no doubt that it is the most important portal of entry for bacteria in their invasion of the parametrium and the uterine appendages.

The inflammatory reactions of the cervix uteri are of great interest and lead to various abnormal epithelial proliferations which have been the subject of extensive investigation in the Stanford gynecological laboratory during the past few years. These formations are of considerable importance in dealing with the incidence of cancer in this organ, and it is generally stated that neglected cervical infections furnish the "irritation" factor which frequently leads to the development of malignancy.

The indiscriminate use of the curette in the treatment of "leukorrhea" is very much to be deprecated. It must be remembered, however, that this operation is of invaluable assistance in the diagnosis of functional changes in the endometrium in cases of abnormal uterine hemorrhage.

EPINEPHRIN AND RELATED DRUGS*

CIRCULATORY RESPONSES THERETO AND MODIFICATIONS BY LOCAL ANESTHETICS

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THE use of cocain as a local anesthetic is frequently accompanied by alarming reactions and even fatalities. The varied symptomatology of these responses indicates complex systemic actions of the cocain. These systemic alterations are not necessarily accompanied by marked symptoms, and therefore may attract little interest until attention is forced on them by a serious reaction. In addition, the sudden, unpredictable occurrence of the reactions, the apparent lack of correlation with the amount of cocain used, and the futility of certain remedies tend to create a rather fatalistic attitude among surgeons toward these side actions. The proper handling of these emergencies must rest on an appreciation of the mechanism of the reactions, and of measures with which they may be treated.

Studies during the last five years in our laboratory have brought out certain new facts which bear on these problems, and it may be in order to summarize briefly these results insofar as they bear on the present topic. In a word, they show that cocain causes complex alterations in the responses of the circulation to certain stimulants, and these alterations in turn indicate fundamental neuromuscular derangements.

In 1910 Fröhlich and Loewi [1] observed that cocain increased the blood pressure response to epinephrin. This was left unexplained and attracted little attention at the time. Since epinephrin is a specific stimulant of the sympathetic nerves (myoneural junctions) and cocain affects the epinephrin action, in otherwise ineffective doses, the increase of blood pressure is due to a sensitization of cocain on the sympathetic nerves. In 1925 the author [2] discovered that cocain not only increased the pressor response of epinephrin, but simultaneously diminished or abolished that to tyramin in the same animal. Before that time tyramin was supposed to act nearly identically with epinephrin. However, this contrast in the actions of these two drugs in the cocainized organism immediately indicated that the sites of their circulatory actions were different, and this difference was revealed through an otherwise ineffective dose of cocain. It showed, further, that the actions of cocain were more complex than had been suspected, since it could simultaneously sensitize and desensitize to similarly acting compounds. The exact mechanism of action of these compounds need not be considered here. Since the initial work, the sensitization-desensitization phenomena have been applied by several investigators to the study of many of these drugs such as ephedrin, phenylaminoethanol, synephrin, etc.

DESCRIPTION OF THE SENSITIZATION-DESENSITIZATION PHENOMENA

In a typical experiment the changes in blood pressure and pulse rate from epinephrin and ephedrin (or other pressor drugs) in a cat or dog are recorded, and then a small dose of cocain is injected subcutaneously. After allowing about fifteen minutes for absorption, the control doses of the two pressor agents are reinjected. The rise of blood pressure from epinephrin is greatly increased in height or duration, or both, and the usual increase in pulse rate is still obtained. But ephedrin now causes little or no effect on either blood pressure or pulse rate. In other words, epinephrin responses are sensitized while ephedrin is desensitized or abolished.

By injecting other compounds, sometimes classed as sympathomimetic amins, in cocainized animals it was found that those drugs which are most closely related chemically to epinephrin, such as the synthetic racemic, dextro- and levo-epinephrin, epinin, and adrenalon, were all similarly sensitized,[3] whereas tyramin,[2] ephedrin,[4] pseudoephedrin,[5] phenylaminoethanol,[6] and other compounds less closely related but classed in this group, were desensitized. Of great interest was the fact that synephrin, the latest of these substitutes, was neither sensitized nor desensitized, but retained its circulatory actions unaltered by cocain.[3]

These altered reactions were not confined to the smooth muscle of the blood vessels, but appeared also in other smooth muscles. Thus, the response of the intestine *in situ* has been shown to be altered simultaneously with the circulatory responses.[2] Similar results with excised intestine have been obtained in experiments now in progress. An antagonism between the broncho-dilator actions of the epinephrin substitutes and cocain has recently been reported.[7]

The dose of cocain required to cause these changes was somewhat variable, as little as five

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milligrams per kilo having been effective, and fifteen milligrams per kilo being uniformly so. It is not known how long the sensitization may persist, but it has been observed as long as three hours after a single administration of cocain in anesthetized animals. This is a considerable period of functional alteration. A point which must be emphasized is that these doses of cocain might not ordinarily be considered toxic, since they caused little or no change in either blood pressure, pulse, or respiration.

Of the local anesthetics thus far studied, cocain has been the only one to cause persistent alterations after subcutaneous administration. Procain, butyn, and saligenin did not alter the circulatory response in a similar manner, when injected subcutaneously.[2] However, it has been reported by Eggleston and Hatcher[8] that procain, B-eucain, apothesin, and certain less important anesthetics do sensitize to epinephrin upon intravenous injection. The sensitizing effects of these local anesthetics on the circulation must be very fleeting, and, as far as we know, nothing has been reported as to their effects on the responses to the other amins. It is hoped to obtain more data on the relative actions of these local anesthetics in future.

MECHANISM OF THE DESENSITIZATION BY COCAIN

The mechanism of the sensitization by cocain to epinephrin has already been discussed in the first part of the paper.

The mechanism of the desensitization is even more interesting and important, although not yet completely understood. Certain pharmacological proofs may be cited. The pressor response to barium, a powerful muscular stimulant, in definitely effective doses is not altered by cocain. The vasoconstrictor action of weak concentrations of barium on the blood vessels of excised organs is abolished or reduced in about one-half the experiments.[2] Since barium stimulates the smooth muscle of the vessels independently of their innervation, this shows that the muscle, when weakly stimulated, is sufficiently depressed by the cocain to prevent its usual responses. The same is true of the comparatively weak muscular stimulants, tyramin,[2] phenylaminoethanol,[6] and ephedrin.[4] These drugs exert typical pressor actions in ergotoxinized animals in which the sympathetic vasoconstrictors are paralyzed. This, of course, correlates with the complementary proof in cocainized animals in which they act differently from epinephrin. That the vascular muscle is not paralyzed is seen from the facts that strong barium stimulation and indirect stimulations by epinephrin cause the usual or increased rises regularly after cocain. This difference between the efficiency of strong and weak stimulants is illustrated time and again in pharmacology. In the case at hand, it simply means that cocain, in otherwise ineffective doses, does poison (depress) sufficiently the smooth muscle or receptive mechanism of the blood vessels so as to make it incapable of responding to weak stimulants; in other words, a sort of vascular "shock." Changes in the functional activity of the cardiac muscle were not the basic causes of the altered responses by cocain, since the high pressures after epinephrin could scarcely have been produced with a heart muscle so depressed as to be unable to withstand the smaller rises from the desensitized amins; that is, the heart was capable of functioning even better than before, against the increased peripheral resistance. Moreover, electrocardiographic studies[9] showed that the doses of cocain used to produce the usual sensitization-desensitization phenomena did not alter the intrinsic nerve mechanisms or muscular responses of the heart, as mirrored in the electrocardiogram.

Central vasomotor actions were readily ruled out since destruction of the brain and spinal cord did not interfere with or prevent the alterations in the circulation caused by cocain.[2,4] Of the peripheral sympathetic nerve mechanisms, *i. e.*, the nerve trunks, endings and myoneural junctions, none is demonstrably depressed, matters that were determined by electrical stimulation of the splanchnics, and also with epinephrin, as already mentioned. Therefore, as the result of direct and indirect tests along different lines it is concluded that the probable seat of the cocain-desensitization of the pressor responses of ephedrin and other amins is, in part at least, in the smooth muscle of the blood vessels, the action being in the nature of a depression or "shock" of the muscle, while the vasomotor nerve endings are made more excitable. Thus, there is a peculiar mixture of depression and apparent excitation of the peripheral neuromuscular mechanism of the blood vessels throughout the body. It is clear that absorbable doses of cocain quickly cause a sustained modification of important bodily functions with potentialities for harm to the organism.

So far as the seat of ephedrin action is concerned, certain authors[11,12] have recently expressed contrary opinions, or doubted the significance of my data for a muscular stimulation. Unfortunately these opinions are rendered untenable by a failure to give adequate and critical consideration of established evidence; these will be dealt with separately.

CLINICAL APPLICATIONS

This complex combination of actions is not only of theoretical interest, but has a direct clinical application, since it always occurs whenever cocain is absorbed, even in otherwise ineffective doses, as in local anesthesia. If a circulatory stimulant should be needed during a reaction accompanying local anesthesia with cocain, the use of epinephrin might be dangerous because of the greatly increased pressor response that will be obtained. The latter might result in sudden cardiac dilation or in apoplexy and thus aggravate the collapse; and the violence of any systemic symptoms from epinephrin would be increased. Resort to one of the epinephrin substitutes would be futile, since either tyramin, ephedrin, or phenylaminoethanol would be ineffective. As far as

I know, the only available compound of this group which would exert its actions unaltered is the new one, synephrin.

Attempts to avoid the toxicity of the cocain-epinephrin combination, used in the nose and throat, by substituting some of the other vaso-constrictors is also unpromising, since the local vaso-constrictor power of ephedrin and phenyl-aminoethanol in the nose is lost in the presence of cocain,[10] just as it is on systemic administration. Similarly, the asthmatic type of reaction in cocain poisoning could not be adequately treated with ephedrin, since cocain antagonizes bronchial muscle responses as well.

Thus, it is seen that what was originally only an interesting pharmacological experiment has important fundamental bearings on the exact determination of the seat of action of the so-called "sympathomimetic" amins, and also strong clinical implications.

CONCLUSIONS

1. Cocain, but not procain, butyn and saligenin, injected subcutaneously in doses (5 to 15 milligrams per kilo) corresponding to those used in infiltration anesthesia, profoundly modifies the circulatory responses to epinephrin, ephedrin, and related drugs.

2. The modifications consist of sensitization, desensitization, or complete abolition, of the circulatory responses (blood pressure and heart rate), according to the drug used.

3. Cocain also modifies the responses of the blood vessels (nose, etc.) to vasoconstrictor drugs after local application, and of the bronchi to bronchodilator agents used systemically.

4. These phenomena are possible whenever cocain is absorbed, even in otherwise ineffective doses, and are of importance in the systemic reactions of cocain poisoning, and in treating accidents of local anesthesia.

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AGRANULOCYTIC ANGINA*

REPORT OF CASE

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DISCUSSION *by Arthur M. Hoffman, M. D., Los Angeles; Albert Soiland, M. D., Los Angeles.*

AGRANULOCYTIC angina is an acute systemic disease of unknown etiology, characterized anatomically by leukopenia, a pronounced reduction or total absence of granular leukocytes in the blood and hematopoietic organs, and an ulcerative or gangrenous inflammation of the buccopharyngeal membranes; clinically by hyperpyrexia, asthenia, and, commonly, an early fatal termination.

HISTORY AND LITERATURE

If we look back upon the literature of former decades, we find as early as 1880 that anginas were mentioned which were marked by the necrotic character of the pharyngeal tonsils and their surrounding tissues, and which terminated fatally for the patients. These anginas were differentiated from diphtheria even at that time. We are reminded of case reports by Wheit in 1885, Cohn in 1893, Noltenius in 1900, Schwarz in 1904, Turk in 1907, and Marchand in 1913, which presented pictures which today are recognized as agranulocytic angina.

It was not, however, until November 1922 when Werner Schultz presented his series of five cases in considerable detail, designating the disease as agranulocytosis, that the medical profession became conscious of the presence of a new clinical syndrome or entity. Since that time reports and discussions have appeared in the literature with increasing frequency under the heading "Agranulocytosis," as used by Schultz, or "Agranulocytic Angina," as used in 1923 by Friedmann. Thus, while in 1922 only one article appeared, there were three in 1923, four in 1924, eleven in 1925, eleven in 1926, twenty-eight in 1927, and nearly forty in 1928. These articles have appeared in the order of frequency from the following countries: Germany, Austria, United States, Canada, France, Netherlands, Italy, and Sweden. No cases seem to have been reported in Great Britain.

In surveying the literature I have collected 168 cases reported as agranulocytic angina, and in the bibliography to this article cite the names of the authors who reported the same. No claim is made of an exhaustive analysis and report of literature, for references to many an article were obtained which were inaccessible, particularly foreign contributions. Could these reports be included, the number of published cases would undoubtedly exceed two hundred.

However, not all cases reported as agranulocytic angina can be accepted as such. Thus, as has been previously pointed out, one of Kastlin's cases was an acute arsphenamin poisoning, and Allan's case with thrombocytopenia and purpura hardly fall within the category of agranulocytic angina.

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